PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/55 — A1

(11) International Publication Number: WO 96/11691

(43) International Publication Date: 25 April 1996 (25.04.96)

(21) International Application Number: PCT/US95/12830

(22) International Filing Date: 13 October 1995 (13.10.95)

(30) Priority Data:
9420747.9 14 October 1994 (14.10.94) GB

(71) Applicant *(for all designated States except US)*: GLAXO WELLCOME INC. [US/US]; 5 Moore Drive, Research Triangle Park, NC 27709 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: HANLEY, Rochelle [US/US]; Glaxo Wellcome Inc., 5 Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agents: LEVY, David, J.; Glaxo Wellcome Inc., Intellectual Property Dept., Five Moore Drive, Research Triangle Park, NC 27709 (US) et al.

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published

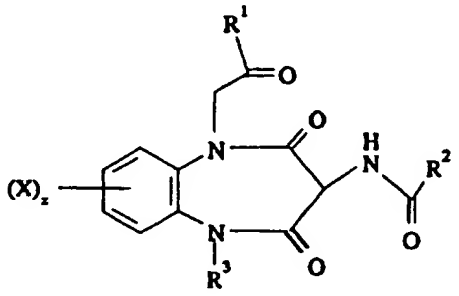
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF 1,5-BENZODIAZEPINE DERIVATIVES FOR THE CONTROL OF GASTRIC EMPTYING IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS

(57) Abstract

The use of a compound of formula (1) or a physiologically salt thereof in the manufacture of a therapeutic agent for the treatment of early non-insulin dependent diabetic conditions.



(1)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

USE OF 1,5-BENZODIAZEPINE DERIVATIVES FOR THE CONTROL OF GASTRIC EMPTYING IN PATENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS

This invention relates to a new medical use of 1,5-benzodiazepine derivatives which exhibit CCK-A agonist activity. More particularly it relates to the use of such compounds to control gastric emptying in patients having an early non-insulin-dependent diabetic condition.

Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system. Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form, its carboxyl terminal octapeptide, CCK-8 (also a naturally occurring neuropeptide), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14- amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH_2 (CCK-4) which is the common structural element shared by both CCK and gastrin.

CCK and gastrin are gastrointestinal hormones and neurotransmitters in the neural and peripheral systems and perform their respective biological roles by binding to particular receptors located at various sites throughout the body. There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B and both are found in the periphery and in the central nervous system.

The CCK-A receptor, commonly referred to as the "peripheral-type" receptor, is primarily found in the pancreas, gallbladder, ileum, pyloric sphincter and on vagal afferent nerve fibers. Type-A CCK receptors are also found in the brain in discrete regions and serve to provide a number of CNS effects. Due to the ability of CCK-8 and Type-A CCK-selective agonists to suppress food intake in several animal species, considerable interest has been generated toward the development of new substances which function as Type-A receptor-selective CCK agonists in order to serve as anorectic agents.

The CCK-B or gastrin receptors are found in peripheral neurons, gastrointestinal smooth muscle and gastrointestinal mucosa, most notably in parietal cells, ECL cells, D cells and chief cells. CCK-B receptors also predominate in the brain and have been implicated in the regulation of anxiety, arousal and the action of neuroleptic agents.

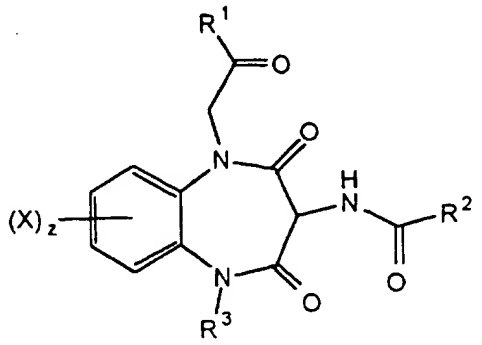
U.S. Patent No. 4,988,692, to Gasc, et al. describes a group of 3-acylamino 1-alkyl-5-phenyl 1,5-benzodiazepine derivatives which behave as cholecystokinin antagonists to reverse or block the effects of the endogenous hormone at its receptors.

US Patent No. 4,490,304 and PTC applications No's WO90/06937 and WO91/19733 describe peptide derivatives that exhibit CCK-A agonist activity. Such compounds have been disclosed for appetite regulation as well as the treatment and/or prevention of gastrointestinal disorders or disorders of the central nervous in animals and, more particularly, humans.

US Patent No. 5,187,154 which is incorporated herein by reference describes the use of the neuropeptide cholecystokinin (CCK) to control gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying. Further the specification teaches that compounds which inhibit gastric emptying may be useful to alleviate or eliminate symptoms associated with early or pre-diabetes. Particular symptoms include elevated blood glucose and insulin levels, insulin resistance, increased susceptibility to infection or glycosuria while also maintaining gastric emptying within normal levels.

We have now discovered that a novel group of 3-amino 1,5-benzodiazepine compounds which exhibit agonist activity for the CCK-A receptor delay or inhibit gastric emptying and thus may be used to treat patents having non-insulin-dependent diabetic conditions and exhibiting rapid gastric emptying.

The present invention thus provides for the use of compounds of the general Formula (I)

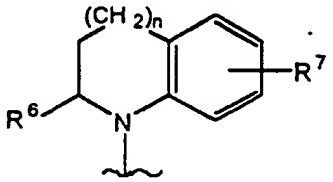


(I)

and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C_{1-4}alkylthio, -O(C_{1-4}alkyl) or halogen;

R^1 is either Formula II or -NR^4R^5.;



(II)

R^2 is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R^8 as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R^9 as defined hereunder or

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino, dimethylamino, -NHR^{10}, 1-pyrrolidinyl or tetrazolyl; or

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C_{1-4} alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino or dimethylamino; or

(4) -NHR^{11} where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;

R^3 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

R^4 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, phenyl, $-(CH_2)_pCN$ or $-(CH_2)_pCOO(C_{1-4}alkyl)$ and R^5 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6} alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C_{1-3}alkyl, optionally substituted by 1 or more fluorine atoms cyano, hydroxy, dimethylamino, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-NH(C_{1-4}alkyl)$, $-COO(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$ pyrrolidino, morpholino or halogen or R^4 is C_{1-2}alkyl and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R^6 is hydrogen or methyl;

R^7 is hydrogen, hydroxy, fluoro, dimethylamino, $-O(C_{1-4}alkyl)$ or $-O(CH_2C_6H_5)$;

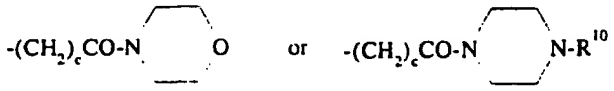
R^8 is $-(CH_2)_bCOOH$;

R^9 is methyl, chloro, nitro, hydroxy, methoxy or $-NHR^{10}$;

R^{10} is hydrogen, acetyl, C_{1-4}alkyl, $-SO_3H$, $-SO_2CH_3$, $-SO_2CF_3$ or $-SO_2C_6H_5$, C_{1-4}alkoxycarbonyl;

R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C_{1-4}alkylthio, $-(CH_2)_cCOOH$, $-(CH_2)_cCOO(C_{1-4}alkyl)$, $-(CH_2)_cSCH_3$, $-(CH_2)_cSOCH_3$, $-(CH_2)_cSO_2CH_3$, $-(CH_2)_cCONH_2$, $-SCH_2COOH$, $-CONH(SO_2CH_3)$, $-CONH(SO_2CF_3)$, $-(CH_2)_cN(C_{1-4}alkyl)2$, $-(CH_2)_cNH(SO_2CF_3)$, $-(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, $-(CH_2)_cSO_2NHCO(C_{1-4}alkyl)$, $-(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $-(CH_2)_cCONHSO_2(C_{1-4}alkyl)$, $-(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-(CH_2)_cOR^{12}$ $-(CH_2)_cNHR^{10}$ or phenyl monosubstituted with $-(CH_2)_c$(tetrazolyl), $-(CH_2)_c$ (carboxamidotetrazolyl) or $-(CH_2)_c$(pyrrolidinyl) or R^{11} is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}$ alkyl), amino, dimethylamino, $-NHR^{10}$;

R^{12} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, $-CH_2C_6H_5$, $-CH_2COOH$, $-CH_2CONH_2$, $-CH_2CONH(C_{1-4}alkyl)$, $-CH_2CON(C_{1-4}alkyl)_2$ or



z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1,

in the manufacture of a therapeutic agent for controlling gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying.

When R^1 represents the group of Formula (II), examples of such a group include those wherein R^6 is hydrogen or more particularly methyl, R^7 is hydrogen, hydroxyl, methoxy, or fluorine, and n is 1.

When R^1 represents the group NR^4R^5 , examples of suitable groups include those wherein R^4 represent C_{3-6} alkyl, such as propyl or isopropyl, cyclohexyl or phenyl and R^5 represents C_{3-6} alkyl, benzyl or phenyl optionally substituted in the para- position by hydroxy, dimethylamino methoxy, trifluoromethyl, fluorine, pyrrolidino or morpholino. Within this group, particularly useful R^1 groups include those wherein R^4 is propyl and, more particularly, isopropyl and R^5 represents phenyl or phenyl substituted in the para-position by groups selected from hydroxy, methoxy dimethylamino, fluorine, or morpholino.

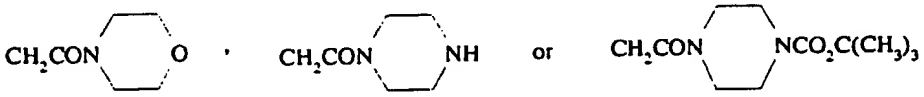
Examples of particularly suitable R^1 groups include those wherein R^1 is the group of Formula (II) wherein R_6 is methyl, n is 1 and R^7 is hydrogen, hydroxy, fluorine or methoxy or R^1 is the group NR^4R^5 wherein R^4 is propyl or isopropyl and R^5 is

phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, trifluoromethyl, dimethylamino, pyrrolidino or morpholino.

When R^2 represents a group selected from indole, indoline, benzofuran, benzothiophene, quinoline or 4-oxobenzopyran, the optional substituent R^9 is conveniently a group selected from hydrogen, methyl, methoxy, hydroxy, nitro or amino and, where appropriate, the optional substituent on nitrogen, (R^8), is -CH_2CO_2H.

When R^2 is an optionally substituted phenyl group, this is conveniently phenyl or phenyl substituted by one or two groups, which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxyl.

When R^2 represents the group NHR^{11}, R^{11} is conveniently phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxycarbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)2$



) or a 7-indazolyl group wherein the N-1 substituent, (R^{10}), is hydrogen.

When R^{11} is a mono substituted phenyl group, the substituted is conveniently in the meta- position.

Examples of particularly suitable R^2 groups includes indole, benzofuran, thiophene, benzothiophene, indoline, quinoline, 4-oxobenzopyran, an optionally substituted phenyl group or the group NHR^{11}. Conveniently, R^2 is selected from the group indole, indoline or benzofuran, an optionally substituted phenyl group or the group NHR^{11}. More particularly, R^2 represents an indole, an optionally substituted phenyl or NHR^{11}.

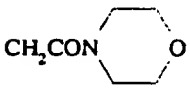
When R_3 represents C_{1-6} alkyl, examples of suitable groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl or isoamyl.

When R_3 represents C_{3-6} cycloalkyl, examples of suitable groups include cyclopropyl, cyclopentyl or cyclohexyl.

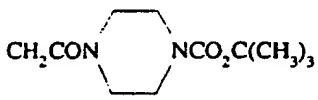
When R_3 represents phenyl, mono or disubstituted by independently with halogen, examples of suitable groups include those wherein the halogen substituent is fluorine e.g., 2-fluorophenyl or 4 fluorophenyl.

Examples of particularly suitable R^3 groups include hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl, and more particularly, phenyl.

A particularly useful group of compounds for use according to the invention include those wherein R^1 represents the group of Formula (II) wherein R^6 is methyl, n is 1 and R^7 is hydrogen, fluorine, hydroxy or methoxy, or more particularly NR^4R^5 wherein R^4 is propyl or isopropyl and R^5 is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino or monopholino; R^2 represents phenyl (optionally substituted independently by one or two groups selected from chlorine, fluorine, hydroxy, amine or carboxy), NHR^{11} wherein R^{11} represents phenyl (optionally substituted by amino, dimethylamino, trifluoromethyl- sulphonylamino, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)_2$,



,


or


and

wherein the substituent is preferably in the meta- position) or an indole wherein the nitrogen atom is optionally subtituted by the group $-CH_2CO_2H$ and the benzo ring is optionally substituted by chlorine, methyl, methoxy, nitro, hydroxy or amino; R^3 represents hydrogen, methyl, cyclohexyl, 2- fluorophenyl or phenyl or, more particularly, 2 fluorophenyl or phenyl; and X represents fluorine and z is 1 or, more particularly, X is hydrogen;

A particularly interesting class of compounds for use in the present invention are those wherein R^2 is an indole group. A preferred group of compounds within this class are those wherein the indole group is substituted on the nitrogen atom by the group $-CH_2CO_2H$ or, more preferably, the nitrogen atom is unsubstituted,

and benzo ring of the indole group is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

A particularly preferred compound for use in the invention which is hereinafter referred to as compound 'A' is:
1H-Indole-2-carboxylic acid {1-[Isopropyl-(4-methoxyphenyl)carbamoyl-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl}-amide and enantiomers thereof.

As provided herein, the term alkyl is generally intended to mean both straight chain and branched chain aliphatic isomers of the corresponding alkyl. For example, C_{1-6}alkyl is intended to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertbutyl, n-pentyl, etc.

The term cycloalkyl, as provided herein, is intended to mean all alicyclic isomers of the corresponding alkyl. For example, the term C_{3-6} alkyl, as provided herein, is intended to include such groups as cyclopropyl, cyclopentyl and cyclohexyl.

The term halogen is intended to mean F, Cl, Br or I.

The term tetrazole as a group or part of a group refers to the (1 H)-tetrazol-5-yl grouping and tautomers thereof.

Those skilled in the art will recognize that stereocenters exist in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of Formula (I) and includes not only racemic compounds but also the optically active isomers as well. When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of Formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids as well as quaternary ammonium acid addition salts. More specific examples of suitable salts include hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, pamoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulphonic, methanesulphonic, naphthalene-2-sulphonic, benzenesulphonic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. References hereinafter to a compound according to the invention include both compounds of Formula (I) and their pharmaceutically acceptable salts and solvates.

CCK-A agonist activity of the compounds of formula (I) may be determined by standard procedures.

The relative affinities of compounds of formula (I) for the CCK-A and CCK-B receptors may also be determined using known conventional procedures such as described by Fornos et al J. Pharmacol Exp. Ther., 1992 261, 1056-1063.

The compounds of formula (I) inhibit or delay gastric emptying and thus may be used to alleviate or eliminate symptoms associated with early or prediabetes, particularly for non-insulin dependent diabetes. Such symptoms include elevated blood glucose and insulin levels, insulin resistance, increased susceptibility to infection and/or glycosuria while also maintaining gastric emptying with normal levels.

The ability of compounds of formula (I) to inhibit or delay gastric emptying may be determined using standard tests. Thus for example rats deprived for food for 18hr were pretreated with the test compound administered i.p at a pre-set time (20 mins) before being given a methyl cellulose meal which was administered by the gavage route. The meal contains a marker element such as Phenol Red. After

specific predetermined time intervals the rats are sacrificed and the amount of the meal in the stomach is determined by measuring the concentration of the mark r substance present. This value is then compared with a control animal which was not pre-treated with the test compound. In this test the preferred compound of formula (I) compound 'A' when administered i.p at doses of 1μmole/kg 20 min before gavage of test meal (1.5% methyl cellulose). completely inhibited gastric emptying 30mins after administration of the test meal. Lower doses of the compound 'A' 0.01 and 0.1μmoles per kg i.p also resulted in a significant reduction in gastric emptying.

According to a further aspect of the present invention, there is provided herein a method for the treatment of a mammal, including man, in particular in the treatment associated with early or prediabetes, particularly noninsulin-dependent diabetes, the method comprising administering to the patient exhibiting rapid gastric emptying an therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per day, e.g., 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that compounds of formula (I) may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. Accordingly, the present invention further provides for a pharmaceutical formulation for use in the present invention comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s)

must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations of the present invention include those especially formulated for oral, buccal, parenteral, implant, or rectal administration, however, oral administration is preferred. For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulphate. The tablets may be coated according to methods well-known in the art. Such tablet coatings conveniently include conventional enteric coatings known to those skilled in the art e.g. cellulose acetate phthalate, polyvinyl acetate phthalate, shellac, styrene maleic acid copolymers, methyacrylic acid copolymers and hydroxypropyl methyl cellulose phthalate.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For oral administration the compounds of formula (I) are preferably formulated as enteric coated tablets or enteric capsules.

Pharmacy

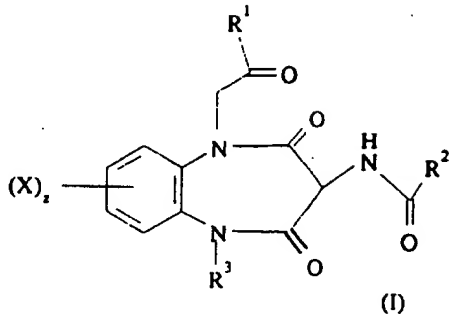
Tablet

Active Ingredient	50 mg
Lactose anhydrous USP	163 mg
Microcrystalline Cellulose NF	69 mg
Pregelatinized starch Ph. Eur.	15 mg
Magnesium stearate USP	3 mg
Compression weight	300 mg

The active ingredient, microcrystalline cellulose, lactose and pregletinized starch are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium starate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches, then coated in a conventional manner with an enteric coating such as cellulose acetate phthalate.

Claims

1. The use of a compound of Formula (1)

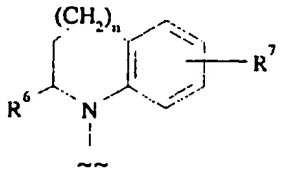


(I)

and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C_{1-4}alkylthio, -O(C_{1-4}alkyl) or halogen;

R^1 is either Formula II or -NR^4R^5.;



(II)

R^2 is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R^8 as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R^9 as defined hereunder or

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino, dimethylamino, -NHR^{10}, 1-pyrrolidinyl or tetrazolyl; or

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C_{1-4} alkyl), -O($CH_2C_6H_5$), -COO(C_{1-4}alkyl), amino or dimethylamino; or

(4) -NHR^{11} where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;

R^3 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

R^4 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, phenyl, -$(CH_2)_pCN$ or -$(CH_2)_pCOO(C_{1-4}alkyl)$ and R^5 is independently C_{3-6}alkyl, C_{3-6}cycloalkyl, C_{3-6} alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C_{1-3}alkyl, cyano, hydroxy, dimethylamino, -O(C_{1-4}alkyl), -O($CH_2C_6H_5$), -NH(C_{1-4}alkyl), -COO(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$ pyrrolidino, morpholino or halogen or R^4 is C_{1-2}alkyl and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R^6 is hydrogen or methyl;

R^7 is hydrogen, hydroxy, fluoro, dimethylamino, -O(C_{1-4}alkyl) or -O($CH_2C_6H_5$);

R^8 is -$(CH_2)_bCOOH$;

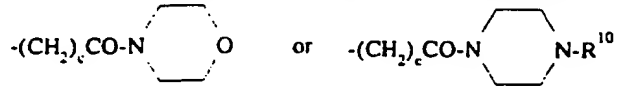
R^9 is methyl, chloro, nitro, hydroxy, methoxy or -NHR^{10};

R^{10} is hydrogen, acetyl, C_{1-4}alkyl, -SO_3H, -SO_2CH_3, -SO_2CF_3 or -$SO_2C_6H_5$, C_{1-4}alkoxycarbonyl;

R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C_{1-4}alkylthio, -$(CH_2)_cCOOH$, -$(CH_2)_cCOO(C_{1-4}alkyl)$, -$(CH_2)_cSCH_3$, -$(CH_2)_cSOCH_3$, -$(CH_2)_cSO_2CH_3$, -$(CH_2)_cCONH_2$, -$SCH_2COOH$, -$CONH(SO_2CH_3)$, -$CONH(SO_2CF_3)$, -$(CH_2)_cN(C_{1-4}alkyl)2$, -$(CH_2)_cNH(SO_2CF_3)$,-$(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, -$(CH_2)_cSO_2NHCO(C_{1-}$

4alkyl), -$(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, -$(CH_2)_cCONHSO_2(C_{1-4}alkyl)$, -$(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, -$(CH_2)_cOR^{12}$ -$(CH_2)_cNHR^{10}$ or phenyl monosubstituted with -$(CH_2)_c$(tetrazolyl), -$(CH_2)_c$ (carboxamidotetrazolyl) or -$(CH_2)_c$(pyrrolidinyl) or R^{11} is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -$O(C_{1-4}$ alkyl), amino, dimethylamino, -NHR^{10};

R^{12} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, -$CH_2C_6H_5$, -CH_2COOH, -CH_2CONH_2, -$CH_2CONH(C_{1-4}alkyl)$, -$CH_2CON(C_{1-4}alkyl)_2$ or



z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

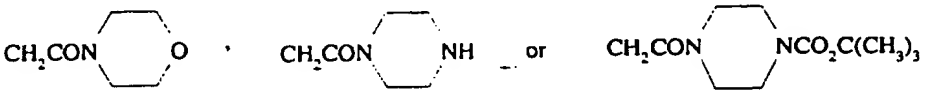
c is 0 or 1.

in the manufacture of a therapeutic agent for controlling gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying.

2. The use of a compound as claimed in Claim 1 wherein R^1 represents the group of Formula (II) wherein R^6 is methyl, R^7 is hydrogen, hydroxyl, methoxy or fluorine and n is 1 or R^1 represents the group NR^4R^5 wherein R^4 represents C_{3-6} alkyl, cyclohexyl or phenyl, and R^5 represents C_{3-6} alkyl or phenyl optionally substituted in the para position by hydroxy, dimethylamino, methoxy, fluorine, pyrrolidino or morpholio.

3. The use of a compound as claimed in Claims 1 or 2 wherein R^1 represents the group NR^4R^5 and R^4 represents propyl or isopropyl and R^5 represents phenyl or phenyl substituted in the para position by a group selected from hydroxy, methoxy, dimethylamino, fluorine, or morpholino.

4. The use of a compound as claimed in any of Claims 1 to 3 wherein R^2 represents a group selected from phenyl (optionally substituted by one or two groups which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxy,) or NHR^{11} wherein R^{11} is phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxycarbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, CH_2CO_2H, CH_2CONH_2, $CH_2CONHCH_3$, $CH_2CON(CH_3)2$



)or 7-indazolyl wherein the N-1 substituted is hydrogen, or R^2 represents an indole group wherein the nitrogen atom is optionally substituted by the group - CH_2CO_2H and the benzo ring is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

5. The use of a compound as claimed in any of Claims 1-4 wherein R^2 represents an indole group which is unsubstituted on the nitrogen atom and in which the benzo ring thereof is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

6. The use of a compound as claimed in any of Claims 1-5 wherein R^3 represents hydrogen, methyl, cyclohexyl,2-fluorophenyl or phenyl.

7. The use of a compound as claimed in any of Claims 1-6 wherein R^3 represents phenyl.

8. The use of a compound as claimed in any of Claims 1-7 wherein X represents hydrogen.

9. The use of a compound as claimed in Claim 1 wherein R^1 represents NR^4R^5 and R^4 represents isopropyl and R^5 represents p-methoxyphenyl; R^2 represents an unsubstituted 2-indole group; R^3 represents phenyl and X represents hydrogen and enantiomers thereof.

10. A method for the treatment of early or pre-non-insulin dependant diabetes which comprises administering to the patient exhibiting rapid gastric

emptying a therapeutically effective amount of a compound of formula (1) or a physioligically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/12830

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,94 24149 (GLAXO INC ;SUGG ELIZABETH ELLEN (US); AQUINO CHRISTOPHER JOSEPH (U) 27 October 1994 see the whole document especially page 9, line 4-11 ---	1-10
A	US,A,5 187 154 (PHILLIPS WILLIAM ET AL) 16 February 1993 cited in the application see the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 1996	20.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCAND J GASTROENTEROL, MAY 1993, 28 (5) P401-7, NORWAY, KONTUREK JW ET AL 'Cholecystokinin in the regulation of gastric acid and endocrine pancreatic secretion in humans.' see the whole document especially page 405, left column, line 11-page 406, right column, line 19 ---	1-10
A	J PHYSIOL PARIS, 1993, 87 (5) P291-300, FRANCE, SCARPIGNATO C ET AL 'Effect of CCK and its antagonists on gastric emptying.' see the whole document especially page 297, left column, line 11-17 -----	1-10

1

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/US 95/ 12830

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although Claim 10 is directed towards a method of treatment of the human or animal body the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: all claims
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are theoretically defined by the formula of claim 1, the search has to be restricted on economic grounds to the prefered compounds and the general concept of the application.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int :onal Application No
PCT/US 95/12830

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9424149	27-10-94	AU-B-	6567594	08-11-94
		AU-B-	6567694	08-11-94
		CA-A-	2158972	27-10-94
		CA-A-	2158973	27-10-94
		WO-A-	9424151	27-10-94
		EP-A-	0694040	31-01-96
		EP-A-	0694039	31-01-96
		FI-A-	954852	12-10-95
		FI-A-	954853	12-10-95
		NO-A-	954090	13-12-95
		NO-A-	954091	13-12-95
US-A-5187154	16-02-93	US-A-	5468727	21-11-95